NTP
National Toxicology Program

Toxicity and Carcinogenesis Studies of β-Myrcene in F344/N Rats and B6C3F1 Mice

(Gavage Studies)

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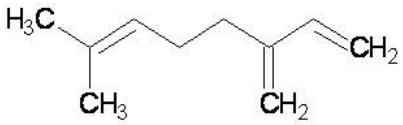
Production, Use and Human Exposure



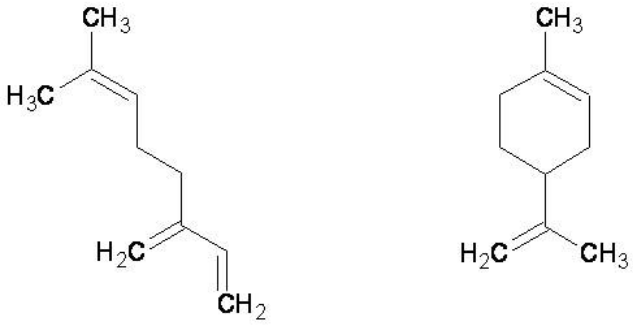
- β-Myrcene, an acyclic unsubstituted monoterpene, is a natural substance found in emissions from various tree species and is also commercially synthesized
- Found in household waste and in indoor air
- Used in the production of aroma and flavor chemicals in cosmetics, soaps, detergents, food and alcoholic beverages
- Also used as medicine for gastrointestinal disturbances and as a sedative, antipyretic and peripheral analgesic
- Humans are exposed via inhalation, ingestion, and dermal contact
- Production volume is large, but reliable figures are not available

Background Information

- Toxicity
  - Humans
    - Irritation, dermatitis, conjunctivitis, asthma-like symptoms
  - Experimental Animals: Low toxicity
    - Oral ALD: 5.06 g/kg in mice, 11.39 g/kg in rats
- Not mutagenic in a variety of assays
- Generally recognized as a safe substance both in its naturally occurring and synthetic forms
- Not regulated by EPA

Rationale for Nomination

- High production volume
- Widespread human exposure
- Lack of toxicity and carcinogenicity data
- Structurally related to d-limonene which induced kidney tumors in male rats



3-Month Study in Rats

- Dose levels: 0, 0.25, 0.5, 1.0, 2.0, 4.0 g/kg in corn oil
- Rationale for dose selection
  - Estimation based on published toxicity studies in rats
  - It was expected that there would be frank toxicity at the high dose concentration and gradation of effects at the lower dose levels

Survival and Final Body Weights of Rats in the 3-Month Study

Dose (g/kg)	0	0.25	0.5	1.0	2.0	4.0
Survival						
Males	10	10	9	9	8	0
Females	10	10	10	9	6	0
Body Weight (% Control)						
Males	-	98	88	89	78	-
Females	-	100	94	94	90	-

N=10

Incidences of Rat Kidney Lesions in the 3-Month Study

Dose (g/kg)	0	0.25	0.5	1.0	2.0
Males					
Tubule Necrosis	0	10** (1.0)[a]	9** (1.1)	10** (1.8)	10** (2.9)
Nephropathy (CPN)	7 (1.0)	10 (1.0)	9 (1.3)	8 (1.0)	9 (1.9)
Nephrosis	0	0	1 (1.0)	10** (1.0)	9** (2.7)
Hyaline Droplets	0	10** (2.0)	9** (2.4)	10** (2.1)	0
Females					
Tubule Necrosis	0	10** (1.0)	10** (1.0)	9** (2.2)	9** (2.4)
Nephropathy (CPN)	1 (1.0)	2 (1.0)	3 (1.0)	4 (1.0)	1 (1.0)
Nephrosis	0	0	0	10** (1.0)	7** (1.1)

N=10; **P≤0.01;
[a]Severity of lesions (1=minimal, 2=mild, 3=moderate, 4=marked)

Dose Selection Rationale for the 2-Year Study in Rats

The highest dose selected was 1 g/kg based on:

- Decreased survival and body weight gains in the higher dose groups
- The severity of the renal tubule degeneration/necrosis seen in the 1 g/kg was not considered sufficient to adversely affect survival
- The clinical chemistry parameters were not affected in 1 g/kg group

Survival and Final Body Weights in the 2-Year Study in Rats

Dose (g/kg)	0	0.25	0.5	1.0
Survival				
Males	29	36	28	0
Females	31	33	28	33
Body Weight (% Control)				
Males	-	109	105	-
Females	-	103	100	89

N=50

Incidences of Rat Kidney Lesions in the 2-Year Study

Dose (g/kg)	0	0.25	0.5	1.0
Males				
Nephrosis	0	42** (1.8)[a]	46** (2.7)	-[b]
Papilla, Mineralization	1 (1.0)	48** (2.1)	40** (1.9)	-
Nephropathy (CPN)	45 (1.2)	48 (2.0)	48 (2.6)	-
Transitional Epithelium Hyperplasia	0	21** (1.4)	19** (1.4)	-
Inflammation, Suppurative, Focal	1 (1.0)	22** (1.0)	22** (1.0)	-
Adenoma or Carcinoma	0	14***	13***	-
Females				
Nephrosis	0	2 (1.0)	27** (1.0)	45** (1.2)
Papilla, Mineralization	5 (1.0)	3 (1.0)	1 (1.0)	0*
Nephropathy (CPN)	26 (1.0)	43** (1.0)	41** (1.3)	44** (1.7)
Transitional Epithelium Hyperplasia	1 (1.0)	12** (1.3)	15** (1.3)	19** (1.2)
Inflammation, Suppurative, Focal	0	1 (1.0)	0	1 (1.0)
Adenoma	0	2	1	3

N=50; *P≤0.05; **P≤0.01; ***P≤0.001;
[a]Severity of lesions (1=minimal; 2=mild; 3=moderate; 4=marked); [b]All males in this group died

3-Month Study in Mice

- Dose levels: 0, 0.25, 0.5, 1.0, 2.0, 4.0 g/kg in corn oil by gavage
- Rationale for dose selection
  - Estimation based on published toxicity studies in rats
  - It was expected that there would be frank toxicity at the high dose concentration and gradation of effects at the lower dose levels

Survival and Final Body Weights of Mice in the 3-Month Study

Dose (g/kg)	0	0.25	0.5	1.0	2.0	4.0
Survival						
Males	10	10	10	10	1	0
Females	10	10	10	10	2	0
Body Weight (% Control)						
Males	-	103	100	91	76	-
Females	-	94	92	97	78	-

N=10

Dose Selection Rationale for the 2-Year Study in Mice

- There were no significant histopathologic lesions observed in the treated groups
- The highest dose selected was 1 g/kg based on adverse effects observed on body weight gains and survival in the higher dose groups

Survival and Final Body Weights in the 2-Year Study in Mice

Dose (g/kg)	0	0.25	0.5	1.0
Survival				
Males	35	35	31	21
Females	39	34	35	17
Body Weight (% Control)				
Males	-	96	90	96
Females	-	97	97	86

N=50

Incidences of Mouse Liver Lesions in the 2-Year Study

Dose (g/kg)	0	0.25	0.5
Males			
Hepatocyte Hypertrophy	1 (1.0)[a]	2 (1.5)	16** (1.7)
Hepatocellular Adenoma	26	41***	43***
Hepatocellular Carcinoma	14	20	28**
Hepatoblastoma	4	6	11*
Adenoma, Carcinoma or Hepatoblastoma	34	45**	48***
Females			
Hepatocyte Hypertrophy	0	0	6* (1.5)
Hepatocellular Adenoma	6	13*	6
Hepatocellular Carcinoma	1	7*	2
Adenoma or Carcinoma	7	18**	8

N=50; *P≤0.05; **P≤0.01; ***P≤0.001;
[a]Severity of lesions (1=minimal, 2=mild, 3=moderate, 4=marked)

NTP Genetic Toxicity Results for β-Myrcene

- No mutagenicity observed in the bacterial assays, with or without S9
- No increase in micronucleated erythrocytes observed in peripheral blood of male or female mice after 3 months of exposure

Conclusions

- Under the conditions of the 2-year gavage studies there was:
  - ***clear evidence of carcinogenic activity*** of β-myrcene in male F344/N rats based on increased incidences of renal tubule neoplasms
  - ***equivocal evidence of carcinogenic activity*** of β-myrcene in female F344/N rats based on increased incidences of renal tubule adenomas
  - ***clear evidence of carcinogenic activity*** of β-myrcene in male B6C3F1 mice based on increased incidence of liver neoplasms
  - ***equivocal evidence of carcinogenic activity*** of β-myrcene in female B6C3F1 mice based on increased incidence of liver neoplasms.
  - Administration of β-myrcene induced nonneoplastic lesions in the kidney of male and female rats, nose of male rats, and liver of male and female mice.